



Pesticide  
Fact Sheet

**Name of Chemical: Clodinafop-propargyl**  
**Reason for Issuance: Conditional Registration**  
**Date Issued: June 6, 2000**

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**1. DESCRIPTION OF CHEMICAL**

Generic Name:	Propanoic acid, 2-[4-[(5-chloro-3-fluoro-2-pyridinyl)oxy]phenoxy]-,2-propynyl ester, (2R)-
Common Name:	Clodinafop-propargyl
Trade Name:	Discover™ Herbicide
EPA Shaughnessy Code:	125203
Chemical Abstracts Service (CAS) Number:	105512-06-9
Year of Initial Registration:	2000
Pesticide Type:	Herbicide
Chemical Family:	Oxyphenoxy acid ester
U.S. Producer:	Novartis Crop Protection, Inc.

**2. USE PATTERNS AND FORMULATIONS**

Application Sites:	Clodinafop-propargyl is registered for use on spring wheat.
Types of Formulations:	97.5% technical product 22.3% end use product (Discover™ Herbicide)
Types and Methods of Application:	Ground application using standard commercial sprayers in 5 to 10 gals. of water per acre.; Aerial application in a minimum of 3 gals. of water per acre.

Application Rates: Use rates on spring wheat range from 3.2 to 4.0 ounces of formulated product (0.05 to 0.0625 pounds of active ingredient, clodinafop-propargyl) per acre; applied with 10.2 to 12.8 ounces of DSV Adjuvant (sold with Discover™ Herbicide) per acre. A single application is made to spring wheat from the 2-leaf stage to emergence of the 4th tiller.

Carrier: Water

### 3. SCIENCE FINDINGS

#### Summary Science Statements

Clodinafop-propargyl is a member of the Oxyphenoxy acid ester chemical class, which includes the active ingredients fluazifop-butyl, fenoxaprop-ethyl, diclofop methyl, quizalofop-ethyl and haloxyfop-methyl. The review of available product chemistry, environmental fate, toxicology, ecological effects and residue chemistry data for clodinafop-propargyl have been completed. The data and estimated risks to human health and the environment from its use on spring wheat are summarized below:

#### Chemical Characteristics

PROPERTY	TECHNICAL	END-USE
Physical State	fine powder	liquid
Color	cream	N/A
Odor	odorless	N/A
Melting Point	48.2 - 57.1C	N/A
Density	1.37 g/cm <sup>3</sup> @ 22C	1.076 g/mL
Solubility (Water)	4.0 ppm @ pH 7, 25C	N/A
Vapor Pressure	2.39 x 10 <sup>-8</sup> mm Hg @ 25C	N/A
Octanol/Water Partition Coefficient	log P <sub>ow</sub> = 3.90 @ 25C	N/A
pH	4.1 @ 25C	4 to 6

**Toxicology Characteristics**

ACUTE TOXICITY (CLODINAFOP-PROPARGYL TECHNICAL)			
GDLN	Study Type	Results	Tox. Cat.
81-1	Acute Oral- Rat	LD <sub>50</sub> =1392 mg/kg (males) 2271 mg/kg (females)	3
81-2	Acute Dermal -Rat, Rabbit	LD <sub>50</sub> >2000 mg/kg	3
81-3	Acute Inhalation- Rat	LC <sub>50</sub> >2.3 mg/L (males or females)	4
81-4	Primary Eye Irritation- Rabbit	Slightly eye irritant	3
81-5	Primary Skin Irritation- Rabbit	Non-irritant	4
81-6	Dermal Sensitization- Rat	Skin sensitizer	Skin sensitizer

ACUTE TOXICITY (END USE PRODUCT: DISCOVER™ HERBICIDE)			
GDLN	Study Type	Results	Tox. Cat.
81-1	Acute Oral- Rat	LD <sub>50</sub> =2231 mg/kg (males) 2240 mg/kg (females)	3
81-2	Acute Dermal -Rat	LD <sub>50</sub> >4000 mg/kg	4
81-3	Acute Inhalation- Rat	LC <sub>50</sub> >3.5 mg/L (males or females)	4
81-4	Primary Eye Irritation- Rabbit	Slightly eye irritant	3
81-5	Primary Skin Irritation- Rabbit	Severe dermal irritant	2
81-6	Dermal Sensitization- Guinea Pig	Skin sensitizer	Skin sensitizer

SUBCHRONIC AND CHRONIC TOXICITY: CLODINAFOP-PROPARGYL	
Guideline No./ Study Type	Results
870.3100/ 28-Day Oral Gavage in Rats	NOAEL < 5 mg/kg LOAEL = 5 mg/kg for M and F based on liver toxicity (enzyme changes),
870.3100/ 13 Week Oral Toxicity in Rodent	NOAEL = M: 0.9 mg/kg; F: 8.2 mg/kg/day LOAEL = M: 120 ppm (8.2 mg/kg/day); F: 1000 ppm (71.1 mg/kg/day) decreased body weight; based on increased liver weights and enzymes (AlPtase); decreased thymus weight (atrophy). Reversed after 28 day recovery period.
870.3100/ 13 Week Oral Toxicity in Mice	NOAEL = M: 0.9mg/kg/day; F: 1.1mg/kg/day LOAEL = M: 7.3 mg/kg/day ; F: 8.6 mg/kg/day based on clinical chemistry; glucose, sodium, and chloride increases and hepatocellular hypertrophy in males and females.
870.3150 90-Day Oral Toxicity in Dogs	NOAEL = M: 0.346 mg/kg/day, F: 1.89 mg/kg/day. LOAEL = M: 1.73 mg/kg/day ; F: 7.16 mg/kg/day based on occurrence of skin lesions.
870.3200 28-Day Dermal Toxicity in Rats.	Systemic NOAEL = 50 mg/kg/day Systemic LOAEL = 200 mg/kg based on dose-related increases in liver weights and clinical signs (piloerection and hunched posture) in male rats. Dermal NOAEL = 1000 mg/kg/day.
870.3700a Prenatal Developmental Toxicity in Rats	Maternal NOAEL = 160 mg/kg/day Maternal LOAEL > 160 mg/kg/day based on lack of effect. Developmental NOAEL = 5 mg/kg/day Developmental LOAEL = 40 mg/kg/day based on increased incidences of bilateral distension and torsion of the ureters, unilateral 14th ribs, and incomplete ossification of the metacarpals and various cranial bones (parietals, interparietals, occipital, and squamosal).
870.3700b Prenatal Developmental Toxicity in Rabbits	Maternal NOAEL = 25 mg/kg/day Maternal LOAEL = 125 mg/kg/day based on mortality, clinical signs and body weight loss Developmental NOAEL = 125 mg/kg/day Developmental LOAEL >125 mg/kg/day

Guideline No./ Study Type	Results
870.3800 Two Generation Rat Reproduction Study	Parental/Systemic NOAEL= 3.2 mg/kg/day. Parental/Systemic LOAEL = 31.7 mg/kg/day based on decrease in body weight gain, reduced food consumption, increased liver and kidney weights and histopathological changes in the liver and renal tubules. Offspring NOAEL = 3.2 mg/kg/day Offspring LOAEL = 31.7 mg/kg/day based on reduced viability, decreased pup body weight and dilatation of renal pelvis. Reproductive NOAEL = 64.2 mg/kg/day. Reproductive LOAEL 64.2 mg/kg/day
870.4100b Chronic Toxicity - Nonrodent	NOAEL = M: 3.38 mg/kg/day; F: 3.37 mg/kg/day LOAEL = M: 15.2 mg/kg/day ; F: 16.7 mg/kg/day based on occurrence of skin lesions, clinical signs, and reduced body weight gain and food consumption.
870.4200b Carcinogenicity - Mice	NOAEL = M: 1.10 mg/kg/day; F: 1.25 mg/kg/day LOAEL =M: 11.0 mg/kg/day; F: 12.6 mg/kg/day based on increase in liver enzyme activity and liver weights. Under the conditions of this study, clodinafop-propargyl induced hepatocellular tumors at 29.6 mg/kg. The chemical was tested at doses sufficient to measure its carcinogenic potential.
870.4300 Chronic/ Oncogenicity in the Rat.	NOAEL = M:0.03 mg/kg/day ; F: 0.03 mg/kg/day LOAEL = M: 0.3 mg/kg/day; F: 0.4 mg/kg/day based on hepatocytic hypertrophy, chronic progressive nephropathy, and tubular pigmentation. Under the conditions of this study, treatment with clodinafop-propargyl increased the incidence of prostate and ovarian tumors in rats at 750 ppm. For males, an increased incidence of prostate adenoma was seen in the high-dose group. The chemical was administered at a dose sufficient to test its carcinogenic potential.
870.5100 Gene Mutation Salmonella and Escherichia/Liver Microsome Test.	Neg. for mutagenicity.
870.5200 Gene Mutation Mutation Test with Chinese Hamster Cells V79	Neg. for mutagenicity.

Guideline No./ Study Type	Results
870.5315 Chromosome Studies; Human Lymphocytes <i>in vitro</i> .	Owing to the conflicting results from the cytotoxicity assessment and the presence of rare complex chromosome aberrations both with and without S9 activation, the study is considered inconclusive.
870.5395 Micronucleus Test (Chinese Hamster)	No clear evidence that clodinafop-propargyl induced a clastogenic or aneugenic effect in either sex at any dose or sacrifice time.
870.5550 DNA Repair Human Fibroblasts.	Compound precipitation was seen at doses 320 g/mL: there was, however, no indication of a cytotoxic effect at any dose. The positive control induced the expected marked increases in UDS. There was, however, no evidence that CGA-184927 in the absence of S9 activation induced a genotoxic response in either trial.
870.5550 DNA Repair Rat Hepatocytes	Compound precipitation was noted at levels 4000 g/mL. Lethality was apparent in the preliminary cytotoxicity test at 94.8 g/mL. The positive control induced the expected marked increases in UDS. There was, however, no evidence that clodinafop-propargyl induced a genotoxic response in either trial.
870.7485 Metabolism and Pharmacokinetics,	The main metabolite was CGA 193469( 76% in male urine). Additional 5% was in the form of taurine conjugate of CGA 193469. Similar distribution was found in feces.
870.7485 Metabolism and Pharmacokinetics,	The major metabolite in urine and feces was determined to be CGA 193469, accounting for about 36% to 47% of the AD for males, and 80% to 85% of the AD for females. In addition, 11 minor metabolite fractions were isolated from urine and feces. Three were further identified as reference materials CGA 193468, CGA 214111 and unchanged clodinafop-propargyl.
Special Study: Determination Of Residues As CGA 193469 In Abdominal Fat After A 3-Month Oral Toxicity Study In Rat.	There was a dose-dependent increase in clodinafop-propargyl residues in fat samples from both sexes taken at the end of treatment (14 weeks) and after the 4-week recovery period (18 weeks). Concentrations of clodinafop-propargyl were higher in male rats at all dose levels tested. With the exception of low-dose group males, for all remaining groups, residues in the fat at 18 weeks had decreased by between 40% - 51.5% of the 14 week value.
Special Study Determination Of Residues As CGA 193469 In Abdominal Fat After 12 Months In Study.	1 ppm and 10 ppm, the concentration of CGA 184927 in the abdominal fat was higher in males when compared to females. At 300 and 750 ppm, the concentration of CGA 184927 in the abdominal fat was comparable between males and females. The results of this study also indicate that the clodinafop-propargyl residue in fat is reduced after 1 year of treatment compared to 3 month treatment.

Guideline No./ Study Type	Results
Special Study: The Effect Of CGA 184927 On Selected Biochemical Parameters In The Rat Liver Following Subchronic Administration.	The effects of clodinafop-propargyl on selected liver enzymes in the rat were similar to the effects seen after subchronic treatment with known peroxisome proliferators (hypolipidemic compounds, phenoxyacetic acid derivatives). Hence, clodinafop-propargyl was considered to most likely be a peroxisome proliferator in the rat liver.
Special Study: Apparently Clonal Thyroid Adenomas May Contain Heterogeneously Growing and Functioning Cell Subpopulations. New Frontiers in Thyroidology, p. 901-905, 1986	The asynchronous growth rate of subsets of cells within the old adenomas as well as the intercellular heterogeneity of the endocytotic response to TSH suggests that clonal thyroid adenomas may acquire new qualities and can modify gene expression via much debated mechanism. The author concludes that the growth of benign thyroid tumors and progression does not require a change in genomic expression in any cell. The apparent heterogeneity of a tumor does not necessarily exclude its monoclonal origin.
Special Study: Assessment of Hyperplastic and Neoplastic Lesions of the Thyroid Gland. Tips, Vol. 8, P. 511-514.	In cell cultures, TSH does not induce proliferation of human thyroid cells, but does stimulate the growth of cells obtained from rat and dog thyroids. Conventional procedures of evaluating carcinogenicity tests by simply counting tumors in rodents treated with high doses, and by mathematical extrapolation to the low doses to which humans are exposed, are not suitable for the proliferative reactions of the thyroid gland. In assessing the human risk, relevant conclusions can only be drawn if the physiological factors of growth control are known, and if the biological mechanisms by which chemicals initiate focal proliferation and support their progression to tumors are considered.
Special Study: Stott, W.t. Chemically Induced Proliferation of Peroxisomes: Implications for Risk Assessment. Regulatory Toxicology and Pharmacology, Vol. 8, P. 125-159, 1988.	The author concludes that a more appropriate MTD of a peroxisome proliferative agent in sensitive species would appear to be based upon evidence of the proliferation of peroxisomes and the induction of peroxisomal enzymes capable of producing an increased intracellular oxidative stress. Exceeding these dosages will only result in a predictable sequence of events leading, ultimately, to tumor formation due to physiological adaptation of the animal to the administered compound rather than from the direct effects of the compound itself.

Guideline No./ Study Type	Results
Special Study Bieri, F. The Effect of CGA 193469, the Free Acid Derivative of CGA 184927, on Peroxisomal - oxidation in Primary Cultures of Rat, Mouse, Marmoset and Guinea Pig Hepatocytes.	This study characterized and compared the <u>in vitro</u> effects of clodinafop-propargyl on selected parameters (i.e., cytotoxicity and induction of peroxisomal beta-oxidation) in primary hepatocytes from various species. The monolayer cultures were treated with medium containing clodinafop-propargyl, CGA 193469 or propargyl alcohol at the appropriate concentrations (0.1 to 100 µg/mL), or solvent controls and incubated for three days. Hepatocytes were then examined for morphological alterations and cell viability. The lactate dehydrogenase (LDH) activity was measured as an indicator of cytotoxicity. In addition, protein content of hepatocytes were measured to determine the membrane damage. Peroxisomal beta-oxidation was measured in hepatocyte homogenates treated with [1-14]palmitoyl-CoA, a peroxisomal enzyme marker. Clodinafop-propargyl-induced cytotoxicity through propargyl alcohol.
Special Study Guyomard, C. (1992). Effects of Cga-193469, the Acid Derivative of Cga-184927, on the Peroxisomal Beta-oxidation in Human Hepatocytes.	Under the conditions of this study, neither CGA 193469 nor bezafibric acid induced peroxisomal beta-oxidation in human hepatocytes, <u>in vitro</u> . However, in the absence of a known concurrent human positive control to validate the test system, (i.e., a substance known to elicit peroxisomal beta-oxidation in human hepatocytes,) this cannot be definitely concluded.
Special Study: Trendelenburg, C. Effects on Selected Plasma Concentrations and Biochemical Parameters in the Liver upon Subchronic Administration to Male Adult Rats.	Clodinafop-propargyl may act as a peroxisomal proliferating agent and alters monooxygenase activity in subfamilies of cytochrome P450 which are known to be involved in the synthesis or catabolism of steroid hormones.

### **Toxicological Endpoints**

The dose at which no adverse effects are observed (the NOAEL) from the toxicology study identified as appropriate for use in risk assessment is used to estimate the toxicological level of concern (LOC). The lowest dose at which adverse effects of concern are identified (the LOAEL) is sometimes used for risk assessment if no NOAEL was achieved in the toxicology study selected. An uncertainty factor (UF) is applied to reflect uncertainties inherent in the extrapolation from laboratory animal data to humans and in the variations in sensitivity among members of the human population as well as other unknowns. An UF of 100 is routinely used, 10X to account for interspecies differences and 10X for intra species differences.



For dietary risk assessment (other than cancer) the Agency uses the UF to calculate an acute or chronic reference dose (acute RfD or chronic RfD) where the RfD is equal to the NOAEL divided by the appropriate UF ( $RfD = NOAEL/UF$ ). Where an additional safety factor (SF) is retained due to concerns unique to the Food Quality Protection Act (FQPA), this additional factor is applied to the RfD by dividing the RfD by such additional factor. The acute or chronic Population Adjusted Dose (aPAD or cPAD) is a modification of the RfD to accommodate this type of FQPA Safety Factor.

For non-dietary risk assessments (other than cancer) the UF is used to determine the LOC. For example, when 100 is the appropriate UF (10X to account for interspecies differences and 10X for intraspecies differences) the LOC is 100. To estimate risk, a ratio of the NOAEL to exposures (margin of exposure (MOE) =  $NOAEL/exposure$ ) is calculated and compared to the LOC.

The linear default risk methodology ( $Q^*$ ) is the primary method currently used by the Agency to quantify carcinogenic risk. The  $Q^*$  approach assumes that any amount of exposure will lead to some degree of cancer risk. A  $Q^*$  is calculated and used to estimate risk which represents a probability of occurrence of additional cancer cases (e.g., risk is expressed as  $1 \times 10^{-6}$  or one in a million). Under certain specific circumstances, MOE calculations will be used for the carcinogenic risk assessment. In this non-linear approach, a “point of departure” is identified below which carcinogenic effects are not expected. The point of departure is typically a NOAEL based on an endpoint related to cancer effects though it may be a different value derived from the dose response curve. To estimate risk, a ratio of the point of departure to exposure ( $MOE_{cancer} = \text{point of departure}/\text{exposures}$ ) is calculated.

The acute and chronic (non-cancer) toxicological endpoints that have been established for clodinafop-propargyl are summarized in the following table.

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary <u>females 13-50 years of age</u>	NOAEL = 5 mg/kg/day UF = 100 Acute RfD = 0.05 mg/kg/day	FQPA SF = 10X aPAD = <u>acute RfD</u> FQPA SF = 0.005 mg/kg/day	Developmental Toxicity Study in Rats] LOAEL = 40 mg/kg/day based on increased incidences of bilateral distension and torsion of the ureters, unilateral 14th ribs, and incomplete ossification of the metacarpals and various cranial bones (parietals, interparietals, occipital, and squamosal)

Exposure Scenario	Dose Used in Risk Assessment, UF	FQPA SF* and Level of Concern for Risk Assessment	Study and Toxicological Effects
Acute Dietary <u>infants and children</u>	NOAEL = 25 mg/kg/day UF = 100 Acute RfD = 0.25 mg/kg/day	FQPA SF = 3X aPAD = <u>acute RfD</u> FQPA SF = 0.083 mg/kg/day	Developmental Toxicity Study in Rabbits LOAEL = 125 mg/kg/day based on increased mortality, clinical signs and body weight loss
Acute Dietary <u>general population</u>	NOAEL = 25 mg/kg/day UF = 100 Acute RfD = 0.25 mg/kg/day	FQPA SF = 1X aPAD = <u>acute RfD</u> FQPA SF = 0.25 mg/kg/day	Developmental Toxicity Study in Rabbits LOAEL = 125 mg/kg/day based on increased mortality, clinical signs and body weight loss
Chronic Dietary <u>all populations</u>	NOAEL = 0.03 mg/kg/day UF = 100 Chronic RfD = 0.0003 mg/kg/day	FQPA SF = 10X cPAD = <u>chronic RfD</u> FQPA SF = 0.00003 mg/kg/day	Chronic Toxicity Study in Rats LOAEL = 0.3 mg/kg/day based on hepatocytic hypertrophy, chronic progressive nephropathy, and tubular pigmentation

\* The FQPA Safety Factor refers to any additional safety factor retained due to concerns unique to the FQPA.

## Carcinogenicity

In accordance with the EPA *Proposed EPA Weight-of-the-Evidence Categories*, August 1999, the Agency's Cancer Assessment Review Committee (CARC) classified clodinafop-propargyl as "likely to be carcinogenic to humans" by the oral route based on the occurrence of prostate tumors in male rats, ovarian tumors in female rats, and liver tumors in both sexes of mice, as well as blood vessel tumors in female mice. For the quantification of human cancer risk, the CARC recommended a linear low-dose extrapolation approach based on the most potent of these tumor types. This approach is supported by possible genotoxic potential and the lack of confirmation of the mode of action of clodinafop-propargyl. The most potent unit risk,  $Q_1^*$  (mg/kg/day)<sup>-1</sup>, of those calculated for clodinafop-propargyl is that for male mouse liver benign hepatoma and/or carcinoma combined tumor rates at 0.129 (mg/kg/day)<sup>-1</sup> in human equivalents.

## Metabolism

In a rat metabolism study, two <sup>14</sup>C labeled variants of clodinafop-propargyl (one labeled on the 2 pyridil carbon and the other uniformly labeled on the phenyl ring, purity >98%) were administered to groups of male Tif:RAI f (SPF) rats, approximately 7 weeks of age by gavage at concentrations of 25.2 mg/kg ( [2-<sup>14</sup>C]pyridil) and 24.6 mg/kg ([U-<sup>14</sup>C]phenyl).

In the urine, the major metabolite was determined to be (R)-2-[4-(5-chloro-3-fluoro-2-pyridinyloxy)-phenoxy]-propionic acid, reference material CGA-193469, accounting for 36.7% to 39.1% of the administered dose (AD). Metabolite fraction U3 hydrolysed to yield fraction U7 (i.e., CGA-193469), when treated with NaOH or HCl. Unchanged clodinafop-propargyl was not identified. In the feces, the major metabolite (fraction F\*7) corresponded to the urinary metabolite U7 (CGA 193469), accounting for 15.7% to 16.9% of the AD. Metabolite fraction F\*8 was determined to be unchanged clodinafop-propargyl, accounting for 0.4% to 1.7% of the AD. In the fat, all metabolites were reportedly acylglycerides, the majority of which were hybrid di- and triacylglycerides, (i.e., approximately 3.5% and 17.0% of the AD, respectively).

## Human Exposures and Risks

### Acute Dietary Risk

Using the tolerance for clodinafop-propargyl in/on wheat of 0.1 ppm and assuming that 100% of the U.S. wheat crop is treated with clodinafop-propargyl, the acute dietary exposure to Clodinafop-propargyl from food will occupy <1.0% of the aPAD for the U.S. population, 7.5% of the aPAD for nursing females 13 years and older, the subgroup of adult females with the highest estimated exposure, and 1.0% of the aPAD for children 1 to 6 years old, the subgroup of infants and children with the highest estimated exposure. In addition, there is potential for acute dietary exposure to Clodinafop-propargyl in drinking water. After calculating Drinking Water Levels of Concern (DWLOCs) and comparing them to the Estimated Environmental

Concentrations (EECs) for surface and ground water, EPA does not expect the aggregate exposure from food and drinking water to exceed 100% of the aPAD.

**Aggregate Risk Assessment for Acute Exposure to Clodinafop-propargyl.**

Population Subgroup	aPAD (mg/kg)	% aPAD (Food)	Surface Water EEC (ppb)	Ground Water EEC (ppb)	Acute DWLOC (ppb)
U.S. Population	0.25	<1.0	0.23 ppb clodinafop- propargyl; 1.1 ppb CGA- 193469	$5 \times 10^{-6}$ ppb clodinafop- propargyl; 0.044 ppb CGA- 193469	$8.7 \times 10^3$
Females 13+ years old	0.01	7.5	Same as above	Same as above	$1.4 \times 10^2$
Children, 1 to 6 years old	0.083	1	Same as above	Same as above	$8.3 \times 10^2$

Chronic Dietary Risk

Using an anticipated residue in wheat of 0.07 ppm (the sum of the limits of quantitation of clodinafop-propargyl and its acid metabolite, CGA-193469) and assuming that 4% of the U.S. wheat crop is treated with clodinafop-propargyl, EPA has concluded that exposure to Clodinafop-propargyl from food will utilize 14 % of the cPAD for the U.S. population and 32% of the cPAD for children 1 to 6 years old, the subgroup of infants and children with the highest estimated exposure. In addition, there is potential for chronic dietary exposure to Clodinafop-propargyl in drinking water. After calculating DWLOCs and comparing them to the EECs for surface and ground water, EPA does not expect the aggregate exposure from food and drinking water to exceed 100% of the cPAD.

**Aggregate Risk Assessment for Chronic (Non-Cancer) Exposure to Clodinafop-propargyl.**

Population Subgroup	cPAD mg/kg/day	% cPAD (Food)	Surface Water EEC (ppb)	Ground Water EEC (ppb)	Chronic DWLOC (ppb)
U.S. Population	0	14	0.0017 ppb clodinafop-propargyl; 0.11 ppb CGA-193469	$5 \times 10^{-6}$ ppb clodinafop-propargyl; 0.044 ppb CGA-193469	0.91
Children, 1 to 6 years old	0	32	Same as above	Same as above	0.21

Dietary Cancer Risk

Assuming residues of 0.07 ppm for wheat and 4% crop treated, EPA estimates that chronic exposure of the U.S. population to clodinafop-propargyl will be 0.000004 mg/kg/day. Applying the  $Q_1^*$  value of  $0.129 \text{ (mg/kg/day)}^{-1}$  results in a food only risk of  $5.3 \times 10^{-7}$ . Following an aggregate dietary (food + water) assessment for lifetime cancer risk, the resulting DWLOC is 0.13 g/L or ppb. The largest EEC value is for surface water chronic exposure to the acid metabolite, CGA-193469 (0.11 ppb). The cancer DWLOC is slightly greater than the highest EEC.

Because the models used to obtain the EECs for clodinafop-propargyl and CGA-193469 are highly conservative screening models not designed specifically for estimating concentrations in drinking water and because of the conservative nature of the food exposure assessment (anticipated residues at LOQ for parent + metabolite), EPA believes this aggregate cancer dietary assessment will not underestimate exposure and that chronic dietary exposure from clodinafop-propargyl residues in food and drinking water will not exceed the Agency's level of concern for lifetime aggregate cancer risk.

### **Environmental Characteristics**

STUDY TYPE	HALF LIFE/OTHER
Hydrolysis (Half Life)	184 days (pH 5) 2.7 days (pH 7) 2.2 hours (pH 9)
Photolysis in Water (Half Life)	N/A
Photolysis on Soil	No significant degradation of parent. Minute photolysis of the acid metabolite (CGA-193469) from organic matter.
Aerobic Soil Metabolism (Half Life)	t-½ (parent) = 0.5 to 1.5 days t-½ (CGA-193469) = 33.6 days
Aerobic Aquatic Metabolism (Half Life)	N/A
Anaerobic Aquatic Metabolism (Half Life)	t-½ = 513 days
Mobility- Leaching (Parent)	mobile in low organic soil to immobile in high organic soil
Mobility- Leaching (Metabolite)	CGA-193469: highly mobile in low to moderate organic soils
Terrestrial Field Dissipation* (Half Life)	CGA-163469 = less than 5 days in the top 10 cm.

### **Potential to Contaminate Drinking Water**

The likelihood of drinking water contamination by the parent compound, clodinafop-propargyl, is low due to high sorption and rapid degradation in the environment. However, the major degradate, CGA-193469, is persistent and highly mobile in low and moderate organic matter soils and has the potential to contaminate drinking water. The Agency used PRZM/EXAMS and SCI-GROW models to estimate residues of Clodinafop-propargyl and CGA-193469 in surface water and ground water and incorporated these estimates into the aggregate risk assessments discussed above under **Human Exposures and Risks**

### **Ecological Characteristics/Risk**

**Terrestrial:** Clodinafop-propargyl is practically nontoxic to slightly toxic to birds ( $LD_{50} = 1455$  mg/kg;  $LC_{50} > 5000$  ppm), slightly toxic to small mammals ( $LD_{50} = 1392$  mg/kg) and practically nontoxic to honey bees ( $LD_{50} > 100$  ug/bee) on an acute basis. The chronic No Observable Effects Concentrations (NOECs) for birds and small mammals are 500 and 50 ppm, respectively.

**Aquatic:** Clodinafop-propargyl is highly toxic to freshwater fish and no more than moderately toxic to freshwater invertebrates ( $LC_{50} = 0.30$  ppm and  $EC_{50} > 2.0$  ppm, respectively). The primary degradate, CGA-193469, is no more than moderately toxic to freshwater invertebrates ( $EC_{50} > 9.2$  ppm).

**Plants:** Tier II seedling emergence tests with clodinafop-propargyl indicate that ryegrass (shoot weight) at 0.031 lb. ai/Acre is the most sensitive species of all monocot and dicots tested. For Tier II vegetative vigor, corn (phytotoxicity) at 0.0048 lb. ai/Acre is the most sensitive species of all species tested. Aquatic plant testing with clodinafop-propargyl indicates that the vascular plant, *Lemna gibba*, and the nonvascular plant, *Navicula pelliculosa*, are the most sensitive species ( $EC_{50} > 2.4$  ppm and 3.0 ppm, respectively).

Based on the estimated environmental concentrations (EECs) of clodinafop-propargyl and its acid metabolite, CGA-193469, the use of Discover™ Herbicide is not expected to pose a risk to non-target organisms, with the exception of non-target plants. There is a concern for endangered terrestrial plants inhabiting dry and semi-aquatic areas adjacent to wheat fields when Discover™ is applied by air.

### **Mechanism of Pesticidal Action**

Clodinafop-propargyl interacts with and inhibits the enzyme, acetyl co-enzyme A carboxylase (ACCase), which is essential for the production of lipids (fatty acids) needed for plant growth. Selectivity is based on the difference in the speed of herbicide breakdown in the crop versus the weeds. Clodinafop-propargyl converts from the ester form to the active acid and then to biologically inactive compounds. Grass weeds such as wild oats and wild millet cannot effectively break down clodinafop-propargyl, so they are controlled as a lethal dose accumulates at the meristematic growing points. A safener, cloquintocet-mexyl, is added to the formulation to accelerate the rate of clodinafop break down in wheat, thus preventing the accumulation of a lethal dose.

## **4. SUMMARY OF REGULATORY POSITION AND RATIONALE**

Available data provide adequate information to support the conditional registrations of Clodinafop-propargyl Technical and Discover™ Herbicide for use on spring wheat.

### **Use, Formulation, Manufacturing Process or Geographic Restrictions**

Restrictions for Use on Spring Wheat:

1. For use on spring wheat (including Durum) grown in Montana, Minnesota, North Dakota and South Dakota.
2. Do not graze livestock or feed forage from treated areas for a minimum of 30 days following application.
3. Do not feed hay for 30 days following application.
4. Do not harvest for 60 days following application.
5. Make only one application per crop season at 3.2 to 4.0 oz. of Discover™ Herbicide (0.05 to 0.0625 pounds of active ingredient, clodinafop-propargyl) per acre.
6. Do not apply through any type of irrigation system.
7. Always use DSV Adjuvant (included in the Discover™ case) with Discover™ Herbicide

**5. SUMMARY OF DATA GAPS**

Toxicology (Acute, Subchronic and Developmental Neurotoxicity; *In vitro* Cytogenetic Assay)  
Residue Chemistry (Plant Metabolism, Residue Analytical Method, Storage Stability, and Magnitude of the Residue Data)  
Ecotoxicity (Avian Reproduction and Seedling Emergence/Vegetative Vigor Studies)  
Environmental Fate (Hydrolysis, Photolysis in Water, Anaerobic and Aerobic Soil Metabolism, Adsorption/Desorption and Field Dissipation Data)

**6. CONTACT PERSON AT EPA**

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Registration Division (7505C)  
Office of Pesticide Programs  
Environmental Protection Agency  
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DISCLAIMER: The information presented in this Pesticide Fact Sheet is for informational purposes only and may not be used to fulfill data requirements for pesticide registration and reregistration.